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# The Cause-and-Effect Relationship Between Type 2 Diabetes Mellitus and Clinically Overt Cryptogenic Cirrhosis: A Matter That Must Be Seriously Revised

Abbas Tavakolian Arjmand,[1,*] and Nasrin Razavianzadeh[1]

[1]Internal Medicine Department, Shahrood Medical School, Islamic Azad University, Semnan, IR Iran

[*]*Corresponding author*: Abbas Tavakolian Arjmand, Khatam-Al-Anbia Hospital, Shahrood Medical School, Islamic Azad University, Semnan, IR Iran. Tel: +98-2333392661, E-mail: Dr.tavakolian@gmail.com

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## *Dear Editor,*

Cirrhosis is defined as the advanced stages of hepatic fibrosis, with characteristic distortion of the hepatic architecture in addition to numerous regenerative nodules. Cirrhosis without an apparent cause is labeled cryptogenic (1, 2). Since metabolic syndrome was identified as a distinct medical entity, and insulin resistance and hyperinsulinemia have been addressed as its fundamental pathophysiologic processes, most cases of cryptogenic cirrhosis have been considered to be linked to non-alcoholic fatty liver disease (NAFLD) of insulin resistance and metabolic syndrome. In this context, type 2 diabetes mellitus (T2DM), a true innocent bystander, was mistaken for a component of active metabolic syndrome or somehow equivalent to it, and with this illusory supposition the medical journals were flooded with papers addressing non-alcoholic steatohepatitis (NASH) and cryptogenic cirrhosis as the monozygotic twin of T2DM (3-9). Underestimated and usually underreported alcohol consumption on the one hand, and profound de novo impairment of glucose tolerance and mild hyperglycemia in chronic liver failure on the other, have resulted in a confusing situation in which one is not able to clearly determine which comes first: T2DM or cirrhosis.

In a study conducted by Younossi et al. (10), of 132 patients with NAFLD, established T2DM was reported in 44 (33%). Of these 44 diabetic subjects with NAFLD, 11 were reported to be affected by full-featured cirrhosis. Based on that paper, it would be supposed that one out of three T2DM patients concurrently has end-stage cirrhosis of the liver. Cusi went further, stating in a review article that approximately 70% of T2DM patients have fatty liver and that NASH is the leading cause of end-stage liver disease in persons with T2DM. The author eventually concluded that NASH is a severe "complication" of T2DM (11). In the Verona diabetes study from Paris (the Mecca of the finest wine in the world), de Marco amazingly suggested that end-stage hepatocellular failure due to cryptogenic cirrhosis was the fourth-leading cause of death in the T2DM population. In another case-control study carried out by Poonawala (12), of 49 patients with cryptogenic cirrhosis, 47% were stated to have T2DM. The authors concluded simply that one out of two cases of cirrhosis of undetermined etiology (cryptogenic) was affected by T2DM, and these two medical entities were assumed to be unequivocally related in a cause-and-effect framework. It seems as though these authors completely ignored the already-settled issue of glucose intolerance and mild diabetes in most cases of end-stage liver disease. In absolute opposition to the above-mentioned studies, in a more reasonable observational cohort study of Japanese workers, NAFLD was introduced as a strong predictor for the development of T2DM (13). We believe that T2DM itself has nothing to do with the development of NAFLD, cryptogenic cirrhosis, or hepatocellular carcinoma. As a matter of fact, both NAFLD and T2DM are the outcomes of an underlying pathophysiologic process: insulin resistance.

We propose that there are two major background variables that have been easily missed in all of these studies: first, the pervasive and inescapable underreporting and underestimation of alcohol consumption that leads to concealed alcoholic hepatitis; second, the newly emerging worldwide pandemic of insulin resistance. To shed further light on this perplexing picture, we designed and carried out a simple but conclusive study. We took advantage of a unique opportunity to investigate the prevalence

of decompensated cryptogenic cirrhosis in a population of T2DM patients living in a confined society in which the production, distribution, and consumption of alcoholic drinks were legally, religiously, and morally banned. In this prospective observational study, a total of 132 overt T2DM patients attending a university hospital diabetes clinic were comprehensively informed about the research project, and those who were interested in participating were included in the study. The research was carried out in a small, interlaced community in which alcohol production, distribution, vending, and consumption were strictly prohibited. We considered any hint of the possibility of surreptitious drinking as an absolute exclusion criterion. Subjects on long-term medications known to cause liver damage or to affect PT, PTT, INR, or platelets were excluded from the study.

A diabetologist, in concert with a hepatologist, thoroughly interviewed and examined all of the participants. Age, sex, duration of diabetes, type of diabetes management, relevant past history, weight, height, and waist circumference were all recorded. The hepatologist was requested to carefully go through a provided list of clinical stigmata of chronic liver disease and cirrhosis, including hepatomegaly, splenomegaly, ascites, spider angiomas, palmar erythema, finger-clubbing, Dupuytren's contracture, collateral veins with caput medusas, jaundice, fetor hepaticus, and asterixis. A panel of blood tests was performed, including CBC, platelet count, ALT, AST, alkaline phosphatase, bilirubin, serum albumin, PT, PTT, INR, HBsAg, HBsAb, HBeAg, HBeAb, and HCVAb. If there were any clinical or biochemical hints of autoimmune hepatitis, all of the routine serologic markers of that condition, including ANA, AMA, ASMA, and ALKM-Ab, were evaluated. Abdominal sonography was performed by an experienced radiologist as the preferred imaging technique to assess the presence of marked liver steatosis. Liver biopsy was considered when marked abnormalities of liver function and high Bonacini scores were encountered. To predict cirrhosis clinically and biochemically, we used Udell's meta-analysis data based on the presence of ascites, platelet count, spider angiomas, and the Bonacini cirrhosis discriminant score. The Bonacini score was calculated based on platelet count, ALT/AST ratio, and INR values (14,15). Data were captured, analyzed and reported as mean $\pm$ SD for quantitative variables and as percentages for categorical variables.

A total of 132 patients with T2DM (43 men and 89 women) finished the entire process of cirrhosis evaluation. The average age of the subjects was 58 $\pm$ 10.9 years (range 31 - 83 years), and the mean duration of diabetes was 7.4 $\pm$ 6 years (range 1 - 25 years). With regard to anthropometric measurements, mean BMI was 34.9 $\pm$ 5.3 kg/m$^2$ (range 21.7 - 43.3 kg/m$^2$) and mean waist circumference was 71.2 $\pm$ 11.5 cm (range 50 - 150 cm). On physical examination, only two subjects had hepatosplenomegaly, one displayed mild jaundice, and two were detected to have ascites. Quite surprising were the results of the liver function tests. Of the 132 diabetic individuals, 95 had liver steatosis (72%), while only 8 (6%) demonstrated abnormal liver enzyme levels; of these, only two demonstrated ALT levels of more than twice the normal range. Markedly abnormal values for PT, INR, and serum albumin were detected in only two patients (1.5%), and according to Udell's meta-analysis cirrhosis criteria, only two of the 132 diabetic subjects could be labeled as having concurrent decompensated cirrhosis, and six were supposed to be affected by NASH. Of the two established cases of chronic liver failure, one (a 60-year-old male of high socioeconomic status) died of recurrent upper GI bleeding from esophageal varices. After his death, his wife recalled, or, more accurately, confessed that her husband had been a heavy drinker for almost 30 years while living abroad. The second case of decompensated cirrhosis was a middle-aged female who tested positive for HCV antibodies.

In contrast to the growing body of evidence that suggests a cause-and-effect relationship between T2DM and cryptogenic cirrhosis, our work clearly casts doubt on this issue. Despite the frank contradiction between our findings and some of the previously mentioned papers, there are few well-designed and carefully conducted studies in close agreement with ours. To test the true mechanism concerning the already-reported increased risk of NAFLD and hepatocellular carcinoma in T2DM, El-Serag et al. carried out a meaningful case-control study and concluded that diabetes mellitus increases the risk of hepatocellular carcinoma only in the presence of other risk factors, such as hepatitis B or C or alcoholic cirrhosis (16). This was exactly what we were trying to prove. We believe that T2DM per se has nothing to do with NASH, cryptogenic cirrhosis, or hepatocellular carcinoma. As a matter of fact, T2DM, liver steatosis, NASH, and cryptogenic cirrhosis are all outcomes of an underlying pathogenic process, the devastating modern human-health catastrophe of insulin resistance syndrome. A crucial issue is the true location of T2DM in the jigsaw puzzle of metabolic syndrome. Considering T2DM as the counterpart of or equivalent to active galloping metabolic syndrome has led to this chronic, deep-seated misunderstanding. T2DM is, indeed, the burnt-out phase of metabolic syndrome, not a component of it. In the setting of galloping metabolic syndrome, NAFLD or NASH requires severe, persistent, and protracted hyperinsulinemia to maintain progression toward cryptogenic cirrhosis. In contrast to galloping NASH, a state of relative insulin deficiency is needed to induce impairment of fasting

plasma glucose (IFG) and then overt T2DM. In other words, the processes of metabolic syndrome and persistent hyperinsulinemia must be loosened up or somehow aborted for T2DM to develop. Thus, from the pathophysiologic point of view, full-featured T2DM and galloping NASH are obviously two distinct medical entities, not related and concordant phenomena. The key concept is that NASH requires ongoing marked hyperinsulinemia to maintain its progression, while T2DM is tied to relative or marked insulin deficiency. How might these two obviously discordant issues relate, however? Based on our results, one might consider the rather high prevalence of fatty liver (72%) and the markedly low rate of steatohepatitis (8%) to be somehow contradictory. We believe that there is a delicate pathophysiologic framework behind this apparent paradox. As a matter of fact, the higher rate of liver steatosis is the persistent sequela of several pre-diabetic years, during which serum insulin concentrations were immensely and constantly high (hyperinsulinemia of metabolic syndrome), whereas the surprisingly low rate of NASH is the result of diminished serum insulin or, more precisely, the consequence of relative insulin deficiency in full-blown hyperglycemia and overt T2DM. Indeed, the evolutionary process of liver steatosis toward steatohepatitis and cryptogenic cirrhosis is considerably aborted once overt T2DM develops.

According to our results and the pathophysiologic principles discussed above, we think it reasonable to suggest that if alcoholic liver disease, as the major and easily overlooked confounding variable, is eliminated from the relevant studies, T2DM per se would seldom lead to frank cirrhosis and overt end-stage liver failure. We believe beyond any doubt that the surging incidence and worrisome prevalence of cryptogenic cirrhosis is a consequence of concealed alcoholic liver disease and the modern-era NASH of metabolic syndrome, not the direct effect of an innocent bystander, T2DM.

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## Footnotes

**Authors' Contribution:** Abbas Tavakolian Arjmand designed the research. The study was conducted by Abbas Tavakolian Arjmand and Nasrin Razavianzadeh. Abbas Tavakolian Arjmand wrote this letter and is responsible for the entire project. All authors read and approved the final manuscript.

**Conflict of Interests:** The authors have nothing to declare with regard to any conflict of interests.

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